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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/790,396 | 03/01/2004 | Shumin Yang | IM-1-C1-PUS-1 | 3337 |

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| EXAMINER |
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OUSPENSKI, ILIA I

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| ART UNIT | PAPER NUMBER |
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1644

DATE MAILED: 04/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/790,396

Applicant(s)

YANG ET AL

Examiner

ILIA OUSPENSKI

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 January 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 65-80 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 65-80 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's amendment, filed 01/18/2005, is acknowledged.

Claims 1 – 64 have been cancelled.

Claims 65 – 80 have been added.

Claims 65 – 80 are pending.

2. This Office Action will be in response to applicant's arguments, filed 01/18/2005.

The rejections of record can be found in the previous Office Action, mailed 09/13/2004.

It is noted that new grounds of rejection are set forth herein.

3. The objection of record to priority claim under 35 USC 119(e) has been withdrawn in view of Applicant's arguments.

4. Applicant's correction of the filing date of priority application 09/646,561 is acknowledged.

Applicant is again reminded to update the status of priority application 09/062,597 (Abandoned).

5. Applicant's statement regarding the absence of co-inventor Sim's signature from Oath or Declaration is acknowledged.

Applicant states that copies of a petition under 37 CFR 1.47(a) filed in the parent application USSN 09/646,561 and of the USPTO decision accepting the parent application without the signature of co-inventor Gek-Kee Sim, as well as a copy of a

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Declaration on Timothy McCutcheon have been attached to Applicant's amendment. However, these documents have not been found attached to Applicant's amendment. Applicant is reminded to submit these documents to complete the record of the instant application.

6. Applicant's statement with regard to inadvertent omission of inventor Karen S. Sellins from Oath or Declaration is acknowledged. A new Oath or Declaration is required.

7. Applicant requests clarification with regard to references listed on IDS 05/17/2004, which were not considered by the Examiner.

According to PTO records (available through Public PAIR system at <http://pair-direct.uspto.gov>) one IDS has been filed in priority application USSN 09/646,561 on 06/24/2002. This IDS list three references, which have been provided in the priority application, and have been considered in the instant application. The remaining forty references listed on IDS filed on 05/17/2004 in the instant application have not been made of record in either the priority application or the instant application.

Applicant is invited to submit copies of these references to complete the instant file. In case these references are not of record due to an oversight on the part of the Office, the examiner apologizes for the inconvenience to Applicant in this matter.

8. Applicant's amendment has obviated the **rejections of record under 35 USC 112, second paragraph**.

9. Applicant's amendment has obviated the **New Matter rejections of record under 35 USC 112, first paragraph**.

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10. Claim rejections under 35 USC 112, first paragraph – Enablement:

Applicant's amendment and arguments have obviated the rejections of record of items (A) – (F).

The rejection of record of item (G), as it applies to the amended claims, is maintained for the reasons of record, as detailed herein.

Claims 66 – 67, 72 – 73, and 78 – 79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition which regulates T-cell mediated immune responses in canids, does not reasonably provide enablement for a composition which regulates T-cell mediated immune responses in non-human animals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant does not appear to have specifically addressed the rejection of record with regard to the above limitation.

The rejection is maintained for the reasons of record, as it applies to the amended claims. The rejection of record is reiterated herein for Applicant's convenience.

The specification discloses the sequences of B7-2 proteins (SEQ ID NOS: 7, 17, 26, 31, and 34) a canine species, *Canis familiaris*. The instant claim encompasses in its breadth a therapeutic composition which regulates T-cell mediated immune responses in any animal, including distant species which possess highly divergent molecules of the immune system.

While it was recognized by those skilled in the art at the time the invention was made that e.g. human B7-2 molecules may regulate responses of human T cells, at least in vitro (see e.g. US Patent No. 6,084,067; see entire document, in particular columns 67 – 69), it was highly unpredictable what, if any, responses would result from combining B7-2 molecules with T cells from other species. For example, Lazetic et al. (J. Biol. Chem., 2002, Vol. 277(41), pp. 38660 – 38668) teach that B7 variants from different mammalian species vary dramatically in their abilities to interact with human CD28 and CTLA-4 molecules (see entire document, especially Figure 2).

In view of the lack of predictability of the art to which the invention pertains, undue experimentation would be required to practice the claimed invention with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed invention, and absent working examples providing evidence which is reasonably predictive that the claimed compositions are effective for regulating T-cell mediated immune responses in animals other than those disclosed in the specification.

Limiting the scope of the claim to recite regulation of T-cell mediated immune response in canines would obviate this rejection.

To summarize, reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. Claim rejections under **35 USC 112, first paragraph – Written Description**: Applicant's amendment and arguments have obviated the rejections of record of items (A) – (F).

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The rejection of record of item (G), as it applies to the amended claims, is maintained for the reasons of record, as detailed herein.

Claims 66 – 67, 72 – 73, and 78 – 79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The following *Written Description* rejection is set forth herein.

Applicant is in possession of a composition which regulates T-cell mediated immune responses in canids.

Applicant is *not* in possession of a composition which regulates T-cell mediated immune responses in non-human animals.

Applicant does not appear to have specifically addressed the rejection of record with regard to the above limitation.

The rejection is maintained for the reasons of record, as it applies to the amended claims. The rejection of record is reiterated herein for Applicant's convenience.

The specification discloses the sequences of B7-2 proteins (SEQ ID NOS: 7, 17, 26, 31, and 34) from only two mammalian species, *Canis familiaris* and *Felis catus*. The instant claim encompasses in its breadth a therapeutic composition which regulates T-cell mediated immune responses in any animal, including distant species which possess highly divergent molecules of the immune system.

While it was recognized by those skilled in the art at the time the invention was made that e.g. human B7-2 molecules may regulate responses of human T cells, at least in vitro (see e.g. US Patent No. 6,084,067; see entire document, in particular columns 67 – 69), it was insufficient information as to what, if any, responses would result from combining B7-2 molecules with T cells from other species. For example, Lazetic et al. (J. Biol. Chem., 2002, Vol. 277(41), pp. 38660 – 38668) teach that B7 variants from different mammalian species vary dramatically in their abilities to interact with human CD28 and CTLA-4 molecules (see entire document, especially Figure 2).

Thus in the absence of a specific and detailed description in applicant's specification of how to effectively practice the claimed invention, and in the absence of working examples providing evidence which is reasonably predictive that the claimed compositions are effective for regulating T-cell mediated immune responses in animals other than those disclosed in the specification, the inventor(s), at the time the application was filed, did not have possession of the claimed invention, other than the composition which, when administered to canines, regulates T-cell mediated immune responses in canines

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

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12. Claims 65 – 80 are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a canine B7-2 protein capable of co-stimulating T cells, does not reasonably provide enablement for a canine B7-2 protein capable of stimulating T cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make an use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention.

Sharpe et al. (Nature Reviews Immunology, 2002, 2 : 116 – 126) describe the two-signal model of lymphocyte activation, in which the specific antigen recognition by lymphocytes (primary signal) is accompanied by co-stimulatory signals, provided by B7 and related molecules (see entire document, in particular, e.g. page 116 left column).

The specification discloses that the canine B7-2 molecules of the invention are capable of co-stimulatory T lymphocytes in the presence of a primary signal (Concanavalin A) (Example 4 at pages 59 – 60). The specification does not provide a sufficient enabling disclosure of a B7-2 molecule capable of stimulating T cells without a primary signal. Therefore, a person of skill in the art is not enabled to make and use a canine B7-2 protein capable of stimulating T cells, commensurate with the scope of the claims.

The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 18 24 (CCPA 1970). "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

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13. Claim rejections under **35 USC 102(a), (b), and (e)**: Applicant's amendment and arguments have obviated the rejections of record.

14. Claim rejections under **35 USC 103(a)**: The rejection of record is maintained for the reasons of record, as it applies to the amended claims.

Claims 65 – 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinelli et al. (of record) in view of US Patent 6,084,067 (of record).

Applicant's arguments have been fully considered, but were not found convincing.

Applicant argues that there is no indication that the protein taught by Pinelli et al. are the same as those of the instant application, since Pinelli does not disclose any sequence for these proteins.

This is not found persuasive, because, as Applicant acknowledges, Pinelli et al. do teach that a B7-2 protein exists on the surface of canine macrophages (page 18 second paragraph). The amino acid sequence of the canine B7-2 protein would be an inherent property of a canine B7-2 protein taught by Pinelli et al.

With regard to the instant limitations of the amended claims, claim 65 is directed to an isolated protein produced by expression from a nucleic acid encoding a canine B7-2 protein, operably linked to a nucleic acid providing means for promoting expression of the first sequence. The claim language, as recited, reads on an endogenous B7-2 gene linked to an endogenous promoter, present in canine macrophages as taught by Pinelli et al. Therefore, the rejection of record is maintained for the reasons of record, as it applies to the amended claims.

The rejection of record is reiterated herein for Applicant's convenience.

Pinelli et al. teach "B7 costimulatory molecules" expressed on macrophages isolated from beagle dogs. The art-recognized definition of B7 costimulatory molecules includes both B7-1 and B7-2 costimulatory proteins, and the use of the word "molecules" in plural by Pinelli et al. demonstrates that both B7-1 and B7-2 costimulatory molecules were included in the teachings. Since B7-1 and B7-2 molecules do not exist in complex with each other, each type of molecule must be present separately on isolated macrophages taught by Pinelli et al. Thus the canine B7-2 protein is inherent in the teachings of Pinelli et al. The B7 protein taught by Pinelli et al. is present on isolated macrophages, it meets the limitation "isolated protein," especially since the claim limitations do not require the protein to be purified.

Pinelli et al. do not specifically teach isolated B7-2 proteins (claim 40), B7-2 proteins lacking at least a portion of the transmembrane domain (claim 41), capable of binding CTLA4 or CD28 or stimulating T-cells (claim 43), encoded by nucleic acids which hybridize to SEQ ID NOS:10 or 20 or are homologous to SEQ ID NOS:9 of 19 (claims 42, 44 – 46, 60, and 61), comprises amino acid sequences homologous to SEQ ID NOS:7 or 17 (claims 47 – 50 and 62 – 64). Pinelli et al. do not specifically teach a therapeutic composition comprising a B7-2 protein which, when administered to an animal, regulates T-cell mediated immune responses in the animal (claims 51 – 52).

The '067 Patent has been discussed supra. The Patent teaches isolated human B7-2 proteins (see entire document, in particular, Figs. 8 and 14); an isolated extracellular domain of B7-2 protein, i.e. a variant of the protein lacking the transmembrane domain (in particular, column 59, lines 35 – 65, and claim 5); binding of B7-2 proteins to CD28 and CTLA4 (in particular, columns 66 – 68), and activation of T cells (in particular, column 69 and Table 2). The '067 Patent also teaches that B7-2 protein and compositions thereof are useful for therapeutically regulating immune responses (in particular, columns 33 – 37), and that compositions may comprise carrier molecules (in particular, column 32 third paragraph).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of the '067 Patent to those of Pinelli et al. to obtain the claimed invention.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because canine B7 costimulatory molecules, including B7-2 proteins, as taught by Pinelli et al., would be expected to therapeutically regulate immune responses in canines, as taught by the '067 Patent for human B7-2 proteins which can be used to therapeutically regulate immune responses in humans. One of ordinary skill in the art would have been motivated to incorporate these proteins into therapeutic compositions including a carrier, since the '067 Patent teaches that such compositions can be used to therapeutically regulate immune responses. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Conclusion: no claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI
Patent Examiner
Art Unit 1644
March 18, 2005


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3/19/05